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REMARKS

The Amendments

The specification and claims are amended to supply the inadvertently missing definition of the Z group from the "A—CZ(B)—$[C(R^1R^2)]_n$—X" formula. Support for this amendment can be found in two of the provisos, i.e., provisos (f) and (g), for the formula making clear that Z includes at least SH and methyl in its definition. Support is further found in the patents cited preceding that formula as support for the source of these complexing agents; see particularly, claim 1 of U.S. Patent No. 5,866,097 (copy attached) supporting that Z was intended to include hydrogen and the same R^4 groups in its definition.

Further, the claims are amended to exclude the iodine radionuclides. This is supported by their disclosure of optionally being used – thus optionally not used – at page 4, second full paragraph, of the specification and by the clear implication in the disclosure that the iodide ions in the invention are not provided by iodine nuclide compounds. This amendment avoids aspects of the prior art as discussed below.

The claims are also amended to incorporate some of the substance of the dependent claims (see, e.g., original claims 5 and 7) defining the targeting agent into the independent claims. This amendment avoids aspects of the prior art as discussed below.

New claim 32 is directed to the species indicated in the Office Action to be allowable, but with the addition of the P2045 specific targeting agent also.

New dependent claims 33-35 are supported by the disclosure in the second full paragraph of page 4.

To the extent that the amendments avoid the prior art or for other reasons related to patentability, competitors are warned that the amendments are not intended to and do not limit the scope of equivalents which may be asserted on subject matter outside the literal scope of any patented claims but not anticipated or rendered obvious by the prior art or

otherwise unpatentable to applicants. Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The Restriction Requirement

The restriction between the composition claims 1-22 and the kit claims 23-31 is respectfully traversed. The basis alleged for the restriction is that the compositions and kits are unrelated because they are not useable together. This is not correct and is not an adequate basis to support a restriction. The kit and the composition contain the same ingredients, one as separate components and one after being mixed. The kit is used to prepare the compositions. They are clearly related. The example given in the cited MPEP section of independent inventions is a shoe and a locomotive bearing, which obviously have no connection at all. Here, the connection between the kits and compositions is quite evident. They are not unrelated or independent, thus, the restriction must be withdrawn.

The Rejection under 35 U.S.C. § 112, paragraph

The rejection of claims 5 and 15 under 35 U.S.C. § 112, second paragraph, is rendered moot by the cancellation of those claims.

The Rejection under 35 U.S.C. § 102

The rejection of claims 1-6 and 11-16 under 35 U.S.C. § 102, as being anticipated by Suzuki (*Appl. Radio.* Article) is respectfully traversed.

Suzuki discloses production of a ^{11}C radiolabeled N-methylspiperone compound (^{11}C-NMS). The compound's formula is shown at page 596 of the article. Suzuki also discloses compositions containing ^{11}C-NMS with potassium iodide. It states that such solutions were

expected to scavenge hydroxyl radicals and it was observed that the radiochemical purity of the ^{11}C-NMS remained constant. See page 597 of the article.

Suzuki fails to disclose a composition, kit or method which combines a radionuclide, iodide ions or an iodide ion-generating compound and a targeting agent wherein the targeting agent is a peptide, oligonucleotide, antibody, peptidomimetic, or a targeting agent bonded to a complexing moiety of the formula A—CZ(B)—$[C(R^1R^2)]_n$—X, as defined in Applicants' claims. Spiperone or N-methylspiperone is not any of these types of targeting agents. Accordingly, Suzuki does not meet the targeting agent element of any of the instant claims. Thus, it does not anticipate the instant claims and the rejection under 35 U.S.C. § 102 should be withdrawn.

Suzuki also does not render the claimed invention obvious under 35 U.S.C. § 103. Suzuki is specific to the use of N-methylspiperone as its, supposed, targeting agent. It would be contrary to the objectives of Suzuki to replace the N-methylspiperone with some other targeting agent, particularly one which is so different from the targeting agents recited in Applicants' claims. Thus, Suzuki also does not support a rejection under 35 U.S.C. § 103.

The Rejection under 35 U.S.C. § 103

The rejection of claims 1-6, 8-9, 11-16, 18-19 and 21-22 under 35 U.S.C. § 103, as being obvious over Blum (*Chest* article) in view of Dean (U.S. Patent No. 6,214,316) in further view of Coy (U.S. Patent No. 5,597,894) is respectfully traversed.

Blum discloses Tc-99m radiolabelled depreotide and its use for chest radiographs to evaluate solitary pulmonary nodules. Blum teaches nothing about providing a composition with iodide ions together with the Tc-99m radiolabelled depreotide.

Dean teaches radiolabelled somatostatin compounds as scintigraphic imaging agents. As the radionuclide, Dean teaches Tc-99m, iodine-125 and iodine-131, among others. Like

Blum, Dean teaches nothing regarding providing a composition with iodide ions along with the radiolabelled imaging agents.

Coy is directed to multi-tyrosinated somatostatin analogs which may be radiolabelled. The reference discloses the use of iodine radionuclides for the radiolabelling. The reference also discloses the use of radiolabelled sodium iodide as the source for such radionuclide; i.e., at col. 25, lines 19-23.

The statement of the rejection alleges that it would have been obvious from Dean that an iodine radionuclide could be used in the Blum invention and that it would have been obvious to use sodium iodide as the source of such radionuclide as disclosed in Coy.

Assuming this analysis is correct – but see below – such a combination of reference teachings would not suggest the claims as amended above. The claims have been amended to exclude the iodine radionuclides. It clearly would not have been suggested to one of ordinary skill in the art to use the sodium iodide source of Coy to provide the radionuclide of a non-iodine nuclide. Coy's iodide compound is obviously only useful for providing iodine nuclides. Thus, the combination suggested in the Office Action would not result in Applicants' invention. Further, such combination would not suggest Applicants' invention because no iodide compound would be necessary when the radionuclide is not based on iodine.

Additionally, Applicants do not believe that the use of the sodium iodide radionuclide source in Coy would result in a composition ultimately containing iodide ions. Coy's process at col. 25, lines 19-34, includes several additional steps after adding the sodium iodide before the radiolabelled compound is produced. It is not evident that the iodide ions would remain in the final radiolabelled composition. Further, Coy provides no teaching that the iodide ions are desirable in the final composition or particularly that they are useful for the advantages

discovered by Applicants' invention. See, e.g., the instant disclosure at page 2, second full paragraph; page 5, first full paragraph; and the Examples at pages 6-7.

For all of the above reasons, it is respectfully submitted that the prior art, considered as a whole, fails to render the claimed invention obvious to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. § 103 should be withdrawn.

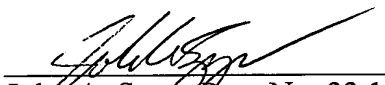
Corrected Application Data Sheet

Some of the information of applicants' originally submitted Application Data Sheet (ADS) was incorrect. A new ADS with the corrections shown underlined is attached hereto and it is requested that the PTO data on this application be corrected to reflect this.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph at page 3, line 16, to page 4, line 6, has been amended to read as follows:

In another preferred, but non-limiting, embodiment the radionuclide is contained in the composition to be stabilized at least partially complexed by a complexing moiety. Examples of complexing moieties and compositions containing complexed radionuclides which can be stabilized according to the invention include those described in each of U.S. Patent Nos. 5,783,170; 5,807,537; 5,814,297; 5,866,097; and 5,262,175 discussed above. One preferred type of complexing moiety is a thiol group-containing moiety such as of the following formula:

$$A—CZ(B)—[C(R^1R^2)]_n—X$$

wherein A is H, HOOC, H_2NOC, (peptide, oligonucleotide, or antibody)-NHOC, (peptide, oligonucleotide, or antibody)-OOC or R^4; B is H, SH or —NHR^3, —$N(R^3)$-(peptide, oligonucleotide, or antibody) or R^4; X is SH or —NHR^3, —$N(R^3)$-(peptide) or R^4; R^1, R^2, R^3 and R^4 are independently H or straight or branched chain or cyclic lower alkyl; n is 0, 1 or 2; and Z is H, SH or R^4; provided that: (a) where B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, or antibody), X is SH and n is 1 or 2; (b) where X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, or antibody), B is SH and n is 1 or 2; (c) where B is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, or antibody)-NHOC, (peptide, oligonucleotide, or antibody)-OOC, X is SH and n is 0 or 1; (d) where A is H or R^4, then, where B is SH, X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, or antibody) and where X is SH, B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, or antibody); (e) where X is H or R^4, A is HOOC, H_2NOC, (peptide)-NHOC, (peptide, oligonucleotide, or antibody)-OOC and B is SH;

(f) where Z is methyl, X is methyl, A is HOOC, H_2NOC, (peptide, oligonucleotide, or antibody)-NHOC, (peptide, oligonucleotide, or antibody)-OOC and B is SH and n is 0; and (g) where Z is SH and X is SH, n is not 0; and wherein the thiol moiety is in the reduced form and the complexing group is preferably capable of being covalently linked to a peptide, oligonucleotide, or antibody.

IN THE CLAIMS:

1. **(Amended)** A composition comprising:

- a radionuclide, excluding I-123, I-125 and I-131, optionally as part of a compound or complex,
- a targeting agent, and
- iodide ions or a compound which releases or generates iodide ions,

where the iodide ions aid in stabilizing the composition against degradation thus maintaining high radiochemical purity of the composition, and,

where the targeting agent:

- is a peptide, oligonucleotide, antibody or peptidomimetic, or
- is a targeting agent bonded to a complexing moiety, of the following formula:

A—CZ(B)—$[C(R^1R^2)]_n$—X

wherein A is H, HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC or R^4; B is H, SH or —NHR^3, —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; X is SH or —NHR^3, —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; R^1, R^2, R^3 and R^4 are independently H or straight or branched chain or cyclic lower alkyl; n is 0, 1 or 2; and, Z is H, SH or R^4; provided that: (a) where B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), X is SH and n is 1 or 2; (b) where X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), B is SH and n is 1 or 2; (c) where B is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC, X is SH and n is 0 or 1; (d) where A is H or R^4, then, where B is SH, X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide,

antibody or small organic compound) and where X is SH, B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound); (e) where X is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH; (f) where Z is methyl, X is methyl, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH and n is 0; and (g) where Z is SH and X is SH, n is not 0; and wherein the thiol moiety is in the reduced form and the complexing group is capable of being covalently linked to the peptide, oligonucleotide, antibody or small organic compound.

7. (Amended) The composition of claim 6, wherein the targeting agent bonded to a complexing moiety is ~~represented by~~ of the formula:

$$A—CZ(B)—[C(R^1R^2)]_n—X$$

wherein A is H, HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC or R^4; B is H, SH or —NHR^3, —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; X is SH or —NHR^3, —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; R^1, R^2, R^3 and R^4 are independently H or straight or branched chain or cyclic lower alkyl; n is 0, 1 or 2; and, Z is H, SH or R^4; provided that: (a) where B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), X is SH and n is 1 or 2; (b) where X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), B is SH and n is 1 or 2; (c) where B is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC, X is SH and n is 0 or 1; (d)

where A is H or R^4, then, where B is SH, X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) and where X is SH, B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound); (e) where X is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH; (f) where Z is methyl, X is methyl, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH and n is 0; and (g) where Z is SH and X is SH, n is not 0; and wherein the thiol moiety is in the reduced form and the complexing group is capable of being covalently linked to the peptide, oligonucleotide, antibody or small organic compound.

11. (Amended) A method for stabilizing a composition comprising: ~~a radionuclide~~

- a radionuclide, excluding I-123, I-125 and I-131, optionally as part of a compound or complex, and
- a targeting agent which:
  - is a peptide, oligonucleotide, antibody or peptidomimetic, or
  - is a targeting agent bonded to a complexing moiety, of the following formula:

$$A—CZ(B)—[C(R^1R^2)]_n—X$$

wherein A is H, HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC or R^4; B is H, SH or —NHR^3, —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; X is SH or —NHR^3, —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; R^1, R^2, R^3 and R^4 are independently H or straight or branched

chain or cyclic lower alkyl; n is 0, 1 or 2; and, Z is H, SH or R^4; provided that: (a) where B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), X is SH and n is 1 or 2; (b) where X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), B is SH and n is 1 or 2; (c) where B is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC, X is SH and n is 0 or 1; (d) where A is H or R^4, then, where B is SH, X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) and where X is SH, B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound); (e) where X is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH; (f) where Z is methyl, X is methyl, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH and n is 0; and (g) where Z is SH and X is SH, n is not 0; and wherein the thiol moiety is in the reduced form and the complexing group is capable of being covalently linked to the peptide, oligonucleotide, antibody or small organic compound,

to prevent or lessen the occurrence of the radionuclide degrading, the method comprising providing iodide ions in the composition.

17. (Amended) The method of claim 16, wherein the targeting agent bonded to a complexing moiety is ~~represented by~~ of the formula:

$$A—CZ(B)—[C(R^1R^2)]_n—X$$

wherein A is H, HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC or

R^4; B is H, SH or —NHR^3, —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; X is SH or —NHR^3, —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; R^1, R^2, R^3 and R^4 are independently H or straight or branched chain or cyclic lower alkyl; n is 0, 1 or 2; and, Z is H, SH or R^4; provided that: (a) where B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), X is SH and n is 1 or 2; (b) where X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), B is SH and n is 1 or 2; (c) where B is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC, X is SH and n is 0 or 1; (d) where A is H or R^4, then, where B is SH, X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) and where X is SH, B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound); (e) where X is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH; (f) where Z is methyl, X is methyl, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH and n is 0; and (g) where Z is SH and X is SH, n is not 0; and wherein the thiol moiety is in the reduced form and the complexing group is capable of being covalently linked to the peptide, oligonucleotide, antibody or small organic compound.

23. (Amended) A kit comprising:

(a) a targeting agent capable of being associated with a radionuclide, which:

- is a peptide, oligonucleotide, antibody or peptidomimetic, or
- is a targeting agent bonded to a complexing moiety of the following formula:

A—CZ(B)—$[C(R^1R^2)]_n$—X

wherein A is H, HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC or R^4; B is H, SH or —NHR^3, —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; X is SH or —NHR^3, —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; R^1, R^2, R^3 and R^4 are independently H or straight or branched chain or cyclic lower alkyl; n is 0, 1 or 2; and, Z is H, SH or R^4; provided that: (a) where B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), X is SH and n is 1 or 2; (b) where X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), B is SH and n is 1 or 2; (c) where B is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC, X is SH and n is 0 or 1; (d) where A is H or R^4, then, where B is SH, X is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) and where X is SH, B is —NHR^3 or —$N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound); (e) where X is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH; (f) where Z is methyl, X is methyl, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH and n is 0; and (g) where Z is SH and X is SH, n is not 0; and wherein the thiol moiety is in the reduced form and the complexing group is capable of being covalently linked to the peptide, oligonucleotide, antibody or small organic compound,

(b) iodide ions or a compound which releases or generates iodide ions, which iodide ions prevent or lessen degradation of the radionuclide due to radiolysis or free ions, and

(c) components for generating a radionuclide, excluding I-123, I-125 and I-131, capable of being associated with the targeting agent,

wherein the kit has two or three compartments, (c) is contained in a separate compartment from (a) or (b) and (a) and (b) may be in the same or different compartments.

28. (Amended) The kit of claim 27, wherein the targeting agent bonded to a complexing moiety is ~~represented by~~ of the formula:

$A—CZ(B)—[C(R^1R^2)]_n—X$

wherein A is H, HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC or R^4; B is H, SH or $—NHR^3$, $—N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; X is SH or $—NHR^3$, $—N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; R^1, R^2, R^3 and R^4 are independently H or straight or branched chain or cyclic lower alkyl; n is 0, 1 or 2; and, Z is H, SH or R^4; provided that: (a) where B is $—NHR^3$ or $—N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), X is SH and n is 1 or 2; (b) where X is $—NHR^3$ or $—N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound), B is SH and n is 1 or 2; (c) where B is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC, X is SH and n is 0 or 1; (d) where A is H or R^4, then, where B is SH, X is $—NHR^3$ or $—N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) and where X is SH, B is $—NHR^3$ or $—N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound); (e) where X is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH; (f) where Z is

methyl, X is methyl, A is HOOC, H_2NOC, (peptide, oligonucleotide, antibody or small organic compound)-NHOC, (peptide, oligonucleotide, antibody or small organic compound)-OOC and B is SH and n is 0; and (g) where Z is SH and X is SH, n is not 0; and wherein the thiol moiety is in the reduced form and the complexing group is capable of being covalently linked to the peptide, oligonucleotide, antibody or small organic compound.

Claims 32-35 have been added.